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Review

The renin-angiotensin system in fructose-induced metabolic syndrome

Fruktozla oluşturulan metabolik sendromda renin-anjiyotensin sistemi

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Abstract

The widespread use of fructose in processed foods is accepted to cause an increase in metabolic syndrome characterized by insulin resistance, abdominal obesity, hypertriglyceridemia, and hypertension. Fructose-induced metabolic syndrome is also associated with various diseases such as type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease (NAFLD). The renin-angiotensin system (RAS) has essential roles in blood pressure regulation, fluid-electrolyte homeostasis, cell growth, and glucose homeostasis. Angiotensin I (Agt I) and angiotensin II (Agt II), which are derived from angiotensinogen by renin and angiotensin-converting enzyme (ACE), respectively, are essential players of RAS. Experimental and clinical studies showed that excessive fructose consumption causes activation in RAS. Increased Agt II in fructose-induced metabolic syndrome initiates insulin resistance by disrupting the insulin signaling pathway and thus predisposes to type 2 diabetes, hypertension and NAFLD. Angiotensin 1-7 (Agt 1-7), which is formed from Agt II by angiotensin-converting enzyme 2 (ACE2) has contra-balancing effects to Agt II as well as regulatory effects on insulin resistance and hepatic fat accumulation.

Keywords: fructose; metabolic syndrome; insulin resistance; renin-angiotensin system

Öz

Fruktozun işlenmiş gıdalarda yaygın olarak kullanılması insülin direnci, abdominal obezite, hipertrigliseridemi ve hipertansiyon ile karakterize olan metabolik sendromun artmasına neden olmaktadır. Fruktozla oluşturulan metabolik sendrom tip 2 diyabet, kardiyovasküler hastalıklar ve alkole bağlı olmayan yağlı karaciğer hastalığı (NAFLD) gibi çeşitli hastalıklara zemin hazırlamaktadır. Renin-anjiyotensin sistemi (RAS), kan basıncının düzenlenmesi, sıvı-elektrolit homeostazı, hücre büyümesi ve glikoz homeostazı üzerinde önemli rollere sahiptir. Renin ve anjiyotensin dönüştürücü enzim (ACE) tarafından anjiyotensinojenden türetilen anjiyotensin I (Agt I) ve anjiyotensin II (Agt II), RAS'ın temel bileşenleridir. Deneysel ve klinik çalışmalar, aşırı fruktoz tüketiminin RAS aktivasyonunu artırdığını göstermiştir. Fruktozla oluşturulan metabolik sendromda artan Agt II, insülin sinyal yolunu bozarak insülin direncini başlatmakta ve böylece tip 2 diyabet, hipertansiyon ve NAFLD'e zemin hazırlamaktadır. Anjiyotensin dönüştürücü enzim 2 (ACE2) tarafından Agt II'den oluşturulan anjiyotensin 1-7 (Agt 1-7), insülin direnci ve hepatik yağ birikimi üzerinde düzenleyici etkilerin yanı sıra Agt II'ye karşı dengeleyici etkilere sahiptir.

Anahtar Kelimeler: fruktoz; metabolik sendrom; insulin direnci; renin-anjiyotensin sistemi

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Introduction

Metabolic syndrome, which is characterized by hyperinsulinemia, hyperlipidemia, abdominal obesity, and hypertension, is becoming a worldwide health problem [1,2,3]. This syndrome affects more than thirty percent of the population in various regions of the world [4-6]. The presence of this syndrom predisposes to the development of many diseases such as type 2 diabetes [7] cardiovascular [7], and non-alcoholic fatty liver disease (NAFLD) [8]. Many factors including high carbohydrate intake, and low physical activity play a role in the development of metabolic syndrome. Insulin resistance, hypertriglyceridemia and abdominal obesity are major indicators in the progression of this syndrome [9]. Insulin released from beta cells of the pancreas activates the insulin receptors and affects glucose and lipid metabolism by phosphorylating proteins involved in the insulin signaling pathway such as insulin receptor substrates (IRS-1 and IRS-2) [10]. Insulin resistance may be mainly attributable to the disruption of this signaling pathway. The changes in the expression of IRS-1 and IRS-2 in metabolic diseases such as type 2 diabetes demonstrated that insulin resistance is one of the most critical factors in developing these diseases [11,12]. Similarly, abdominal obesity or visceral fat accumulation is one of the underlying causes of metabolic syndrome [13]. The adipose tissue distribution is crucial in metabolic syndrome [14]. Particularly, the increase in abdominal fat mass is a risk factor for metabolic and cardiovascular diseases [15,16,17].

Changing dietary habit is one of the responsible factors for developing metabolic syndrome [18]. In today's diets, the consumption of sugars containing fructose has become quite common [19]. High-fructose intake in the diet suppresses the insulin signaling pathway and causes insulin resistance [20-24]. Fructose metabolism, unlike glucose, is not suppressed by the feedback mechanism, and de novo lipogenesis is directly stimulated by the monosaccharide [25,26]. Therefore, fructose induces lipogenesis and leads to worse results in metabolic syndrome compared to other sugars [25-27]. The observation of an increase in visceral adipose tissue with the consumption of fructose-sweetened beverages, has proven that fructose is closely associated with metabolic syndrome and abdominal adiposity [27-29]. Therefore, high fructose administration has become a common dietary method for conducting an experimental metabolic syndrome model in animals [30].

The renin-angiotensin system (RAS) plays a vital role in regulating blood pressure and fluid-electrolyte balance [31]. Angiotensinogen, which is produced in the liver as a precursor compound of this system, is converted to angiotensin I (Agt I) by the renin enzyme released from the kidney. Then, the angiotensin-converting enzyme (ACE) in the lung converts Agt I to Agt II [31,32]. Agt II exerts the well-known effects such as vasoconstriction, promotion of cell growth and inflammation by activating the angiotensin II type 1 receptor (AT1R). Angiotensin II type 2 receptors (AT2R) has opposite effects to Agt II on AT1R [33]. Angiotensin 1-7 (Agt 1-7), another critical RAS component, is formed from Agt II by the angiotensin-converting enzyme 2 (ACE2). This component has a contra-balancing effect to Agt II via Mas receptor (MasR) [31]. In addition to being systemically expressed, RAS components are locally presented in various tissues such as adipose, heart, kidney, pancreas, and brain [33-35]. Increased local RAS activity contributes to systemic RAS action and accelerate the effects of this system. High-fructose consumption activates local and systemic RAS components [36]. In fructose-induced metabolic syndrome, increased RAS activity is one of the fundamental causes of exacerbation of insulin resistance [26], cardiovascular side effects [26,37], and NAFLD [38]. Here, we presented preclinical and clinical evidence showing the effects of systemic and tissue components of RAS in the progression of fructose-induced metabolic syndrome and its complications.

1.The effect of the renin-angiotensin system on insulin resistance in fructose-induced metabolic syndrome

Insulin is an important hormone synthesized in the β cells of the pancreas and stimulates glucose utilization in peripheral tissues [39,40]. This hormone initiates the intracellular insulin signaling pathway by phosphorylating IRS-1 and IRS-2 after binding to the insulin receptor. Phosphorylated IRS-1 and IRS-2 activate phosphoinositide-3-kinase and convert phosphoinositol diphosphate to phosphoinositol triphosphate. Phosphoinositol triphosphate activates protein kinase B (Akt). Akt translocates GLUT4 to the plasma membrane and promotes glucose transportation, regulating glycogen synthesis and gluconeogenesis [10,12,40,41]. In metabolic syndrome, this signaling pathway of the insulin hormone is suppressed and the glucose utilization in the target tissue is not as much as in the physiological state. This situation is determineted as insulin resistance [42]. Studies have demostrated that high-fructose diet causes insulin resistance by reducing the expression of proteins in the insulin

signaling pathway such as IRS-1 [22-24], IRS-2 [23], and Akt [22] in various tissues. The increase in RAS activation by fructose consumption is one of the factors that play an important role in the occurrence of these effects. Supportingly, the fact that high-fructose intake induces the gene expression of various RAS components such as angiotensinogen, Agt II, ACE, AT1R in various studies [43,44]. RAS is involved in the etiology of insulin resistance, which is an important determinant of metabolic syndrome. In particular, Agt II, which is increased by RAS activation, decreases phosphoinositide-3-kinase sensitivity by increasing serine phosphorylation and decreasing tyrosine phosphorylation of IRS-1. This condition reduces Akt formation, as well as the transport of glucose transporters to the membrane and glucose entry into the cell [36,45]. At the same time, increased level of vasoconstrictor Agt II decreases glucose uptake by decreasing blood flow to insulin-sensitive tissues [30]. Based on this information, Rabie and colleagues have indicated that in a rat model of metabolic syndrome induced by a 60% high-fructose diet for twelve weeks, blocking the RAS at renin and Agt II receptor levels by aliskiren and telmisartan improved plasma glucose levels and insulin sensitivity. In addition, it has been shown that the gene expression levels of peroxisome proliferator-activated receptor-α (PPAR-α) and peroxisome proliferator-activated receptor-γ (PPAR-γ), which are important transcription factors in insulin sensitivity, were increased in rats treated with aliskiren and telmisartan [46]. Similarly, in an in vivo study, a 60% high-fructose diet for eight weeks was used to induce a rat model of metabolic syndrome for evaluating the effects of aliskiren, a direct renin inhibitor, on insulin sensitivity. The preventive and treatment effects of renin inhibition were assessed by administering aliskiren at the first day of the experiment or the fourth week of the experiment. The results show that renin inhibition increases insulin sensitivity by lowering glucose as well as insulin levels measured on 56. days in aliskiren-administered groups [47]. In another study evaluating acute and chronic losartan (angiotensin receptor antagonists) treatment, rats were administered a 60% fructose diet for two weeks. The findings of study indicated that chronic losartan treatment reduced hyperinsulinemia in fructose-fed rats [48]. Similarly, the effects of delapril (an ACE inhibitor) and TCV-116 (angiotensin receptor antagonists) were studied in rats fed a 66% fructose diet and in essential hypertensives individuals. Both ACEI (angiotensin-converting enzyme inhibitor) and ARB (angiotensin receptor antagonists) treatments improved insulin resistance as assessed by the steady-state glucose level in fructose-fed rats or by the glucose-clamp method in individuals with essential hypertensives [49]. These studies demonstrate that inhibition of Agt II formation or receptor interaction improves insulin sensitivity in fructose-dependent metabolic syndrome.

Agt 1-7 is another important RAS component formed from Agt II by the ACE2 enzyme. This component improves metabolic parameters such as glucose homestasis and insulin sensitivity by balancing the effects of Agt II through Mas receptors. An animal study evaluated whether Agt 1-7 improves metabolic parameters in 10% fructose-fed rats. After six weeks diet of 10% fructose, the authors measured systolic blood pressure and the levels of insulin, triglyceride, and glucose, they also evaluated the insulin signaling pathway at the level of IR/IRS-1/PI3K/Akt. Fructose-fed rats displayed hypertension, hyperinsulinemia, and hypertriglyceridemia as well as decreased insulin signaling through the IR/IRS-1/PI3K/Akt pathway. However, six weeks of Agt 1-7 treatment normalized all alterations, including insulin resistance, via a mechanism that could cover the modulation of insulin signaling [50]. In a study examining the effects of chronic Agt 1-7 treatment, the rats were fed a high fructose/low magnesium diet for 24 weeks. After six months, improved glucose tolerance, better insulin sensitivity, and lower serum triglycerides were observed in Agt 1-7-treated rats compared to control groups. Similar effects were observed in rats exposed to a high fructose diet for five months followed by short-term (4 weeks) treatment with Agt 1-7 [51]. In another study examining the effect of Agt 1-7 in a metabolic syndrome model, the rats were fed a 10% fructose diet for 6 weeks. During the last 2 weeks of the high fructose feeding period, rats were treated with Agt 1-7 and Mas receptor antagonist A-779. The results of the study showed that Agt 1-7 treatment reduces systolic blood pressure, plasma insulin and triglyceride levels, which are increased by high-fructose diet. Furthermore, it was observed that Agt 1-7 treatment increased the phosphorylation of insulin signaling pathway components such as Akt, and AS160 (Akt substrate) and GSK-3β (glycogen synthase kinase-3β) which is responsible for glycogen synthase in skeletal muscle, adipose tissue, and liver. Also, the reversing effects of Mas receptor antagonist A-779 suggests that Agt 1-7 ameliorates the metabolic effects through the Mas receptor [52].

On the other hand, Agt II activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which leads to increased production of reactive oxygen species (ROS) by

AT1R effects [45,46,53,54]. This activates the Nf-kB pathway, which consequently increases the transcription of cytokines such as TNF-α [46] (Figure 1). These cytokines further inhibit insulin signaling by increasing the cytokine signal 3 expression [53]. In a study in rats fed a 60% fructose diet for eight weeks, it was investigated whether fructose consumption induces the NADPH oxidase enzyme, which increases intracellular ROS levels, by RAS activation. In the study, it was determined that plasma insulin, Agt II, triglyceride and vascular NADPH enzyme levels have increased in fructose-fed rats, which reversed by losartan treatment. In AT1a knock out rats, it was observed that the levels of p22phox, gp91phox and p67phox subunits of NADPH oxidase enzyme have decreased in fructose-fed rats. These results suggest that the increased NADPH enzyme activation with fructose consumption is mediated by RAS [54]. In the comparison of the effects of renin inhibition and angiotensinogen receptor blockade, both aliskiren and telmisartan improved blood glucose, plasma insulin, HOMA-IR, insulin sensitivity, dyslipidemia, hypertension, oxidative stress, and inflammatory parameters such as Nf-kB and TNF-α leves in the fructose-fed rats [46]. These findings suggest that inhibition of any component of the RAS pathway alleviates insulin resistance of fructose-fed rats through improving of insulin signaling and inflammation and oxidative stress.

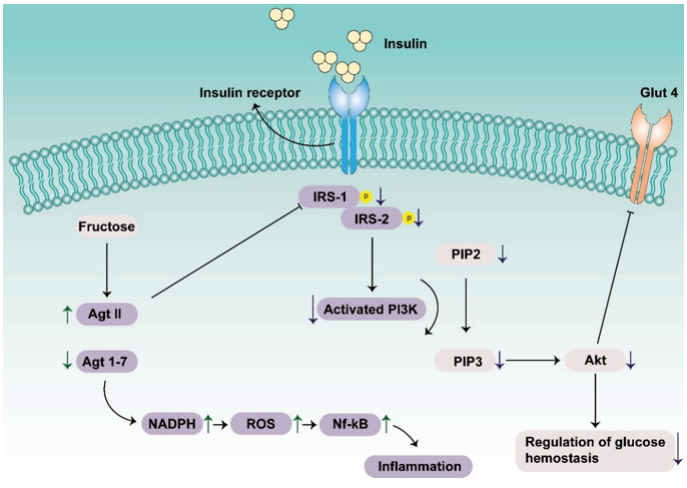

Figure 1. Schematic representation of the effects of Agt II, which increases with fructose consumption, on insulin resistance. Agt II: Angiotensin II, Agt 1-7: Angiotensin 1-7, IRS-1: Insulin receptor substrate-1, IRS-2: Insulin receptor substrate-2, PI3K: Phosphoinositide-3-kinase, PIP2: Phosphoinositol diphosphate, PIP3: Phosphoinositol triphosphate, Akt: Protein kinase B. NADPH: Nicotinamide adenine dinucleotide phosphate, ROS: Reactive oxygen species

2. Relationship between the renin-angiotensin system and abdominal obesity in fructose-induced metabolic syndrome

The distribution of adipose tissue is more important than the amount of adipose tissue in metabolic diseases [55]. Determining the fat distribution is highly important although body mass index (BMI) is seen as a primary tool in evaluating the risk possibilities of metabolic syndrome [16]. In particular, quantitative analysis of visceral fat distribution has been found to be crucial for the assessment of obesity-related metabolic and cardiovascular risks [56]. Abdominal obesity, a dangerous fat accumulation, is associated with an increased risk of multiple chronic diseases, including diabetes, coronary hearth disease, hypertension and stroke [57]. It has been shown in various studies that high-fructose consumption increases the accumulation of abdominal fat [58,59]. In a study in which female rats were fed isocalorically with fructose or glucose solutions for seven months, it was found that fructose feeding produced an increase in body weight due to hyperleptinemia and white adipose tissue hypertrophy [29]. In assessement of subcutaneous and visceral adipose tissue changes in a fructose-induced metabolic syndrome model of adult rats, it was shown that a high-fructose diet increased non-esterified fatty acids, lipid peroxidation, epididymal and mesenteric white adipose tissue volumes. Although mean adipocyte volume in subcutaneous adipose tissue was lower, adipocyte volume in intraabdominal adipose tissue was higher in rats fed a high-fructose diet compared to control rats. Also, the high-fructose diet decreased the ratio of p-Akt/Akt in rats. These data suggest that a high-fructose diet is a severe risk factor for metabolic diseases [60]. It is also known that high-fructose consumption increases the expression of RAS components such as angiotensinogen, Agt II, ACE, AT1R in adipose tissue [44]. For instance, it was determined that rats fed a 66% fructose diet for 14 days had increases in blood pressure and adipose tissue AT1R mRNA levels [61]. Molecular studies, showed that angiotensinogen, ACE, and AT1R gene expressions were increased in the adipose tissue of rats fed a 60% fructose diet for eight weeks [44]. In addition, a 10% fructose diet for nine weeks increased AT1R but decreased AT2R expressions [62]. The results of these studies show that RAS mediators in adipose tissue are involved in fructose-induced metabolic syndrome.

Activated RAS components promote adipocyte differentiation by reducing adipocyte number but increasing adipocyte size. RAS blockade was suggested to improve differentiation of adipocytes [63]. A study tested the effect of RAS blockade

on insulin sensitivity and adipocyte size in fructose-fed rats. Fructose-fed rats had a lower insulin sensitivity, which was recovered by the treatments with temocapril and olmesartan, an angiotensin-converting enzyme inhibitor, and Agt II type 1 receptor blocker, respectively. Also, adipocyte sizes showed negative correlations with the insulin sensitivity [64]. Aliskiren-mediated renin inhibition significantly decreased Agt II level in visceral fat and adipocytes of fructose-fed rats [65]. Similarly, the administration of captopril significantly reduced abdominal fat accumulation in rats fed a 60% fructose diet for 20 weeks [66].

3. Development of hypertension in fructose-induced metabolic syndrome

Hypertension is one of the characteristic features of the metabolic syndrome. It is known that systolic hypertension occurs in metabolic syndrome induced by high-fructose diet [67,68]. Numerous studies have shown that fructose feeding in rodents increases arterial blood pressure [69-73]. A relationship between fructose -sweetened beverages and hypertension has also been established in various clinical studies [74-77]. A study investigating the effects of 60 grams of fructose or glucose on blood pressure in healthy young adults showed that fructose significantly increased blood pressure, heart rate, and cardiac output compared to glucose [76]. Similarly, another study reported that consuming 200 grams of fructose daily for two weeks increased systolic and diastolic blood pressure in 74 healthy men [77]. RAS is one of the essential mediators in regulating blood pressure [31]. Agt II, the main component of the RAS, plays an essential role in the pathogenesis of hypertension associated with fructose-induced metabolic syndrome [78]. Agt II via binding to AT1R produced a vasoconstriction in fructose-fed hypertensive rats [79]. Studies have shown that both Agt II [78] and AT1R [80] receptors are upregulated in fructose-fed rats, suggesting that the functional interactions of Agt II and AT1R increase systolic blood pressure in fructose-induced metabolic syndrome [79]. At the molecular level, a 60% fructose diet inducing changes in AT1R mRNA levels in rat aorta and heart tissue has been found to cause hypertension. Moreover, ACE inhibitor captopril reversed this event by decreasing aortic AT1R mRNA level [81]. In a study investigating Agt II produced by chymase, fructose-fed rats were shown to have increased systolic, diastolic and mean blood pressures [82]. Another study examining fructose-dependent variations of cardiac and aortic RAS components indicated that administrating 10% fructose solution for nine weeks increases blood pressure and ACE and AT1R expressions, but decreases ACE2 and AT2R expressions in male rats [83]. A 66% fructose diet in rats for 14 days increased cardiac hypertrophy, and blood pressure. Angiotensin receptor bloker treatment decreased the hypertrophy, and blood pressure suggesting a central role for Agt II signaling in fructose consumption [84]. In the other study, it has been also shown that a 60% fructose diet for eight weeks led to left ventricular hypertrophy in rats with severe aortic regurgitation possibly through the hypertrigliseridemia [85]. The acute and chronic losartan treatments reduced the cardiac hypertrophy observed in fructose-fed rats suggested that Agt II mediates mitogenic effects in this dietary intervention [48]. In addition, fructose appears to increase salt and Agt II sensitivities by modulating the Na/H channel activity in the proximal tubule thereby causing hypertension [86]. All together, these studies revealed that RAS is essential in hypertension observed in fructose-induced metabolic syndrome.

4. NAFLD in fructose-induced metabolic syndrome

NAFLD, which is considered the liver component of the metabolic syndrome, includes a wide range of pathological conditions from simple steatosis to nonalcoholic steatohepatitis, fibrosis and cirrhosis [87]. The global prevalence of this disease is estimated to be around 32% [88]. The primary manifestation of the disease is accumulated triglyceride droplets (>5%) in the cytoplasm of hepatocytes [89,90]. Triglyceride accumulation in the liver is directly affected by carbohydrate metabolism [91]. In particular, increased fructose intake has been heavily implicated in NAFLD [92]. Studies have shown that high-fructose flow to the liver accelerates the development of the disease by disrupting normal hepatic carbohydrate metabolism and causing de novo triglyceride synthesis [93,94]. At the same time, the role of RAS is very important in the development of NAFLD. While insulin resistance and de novo lipid synthesis occur in the first stage of this disease, inflammation plays a major role in the second step. Increased Agt II expression causes the development of the disease by increasing both insulin resistance and de novo lipid synthesis as well as inflammation [95] (Figure 2). There are various studies showing increased RAS system activity in the presence of NAFDL [38,96]. In a study 15% fructose diet for 21 weeks it was reported an inrease in hepatic steatosis

and liver weight as well as serum triglyceride, insulin, ACE, and Agt II levels. Moreover, at the molecular level, the fructose diet affects transcription factors such as sterol regulatory element-binding proteins 1 and 2 (SREBP-1c, SREBP-2), PPARα and fatty acid synthase (FAS) levels. All these showed that fructose consumption increases RAS components' levels and insulin resistance and thus leads to the development of NAFLD [38]. In addition, the ACE2/Agt 1-7/Mas axis is thought to have regulatory effects on NAFLD formation by inhibiting hepatic insulin resistance and liver lipogenesis [96]. A rodent study indicates that a rat model of NAFLD, created by a 20% fructose diet for eight weeks, appears to have a high ratio of liver weight/body weight and increased serum and hepatic triglyceride levels and fat droplet numbers in the liver. In line with this, Attia et al. suggest that the fructose diet enhances the Agt II protein level and reduces the protein levels of ACE2 and Agt (1-7) and Mas receptors. While fat accumulation in the liver is considered the first step in the development of NAFLD, as it has been mentioned above, inflammatory cytokines and oxidative stress are also important players in the pathogenesis of NAFLD. Abnormal cytokine production and decreased antiinflammatory RAS components such as Agt 1-7 may also contribute to NAFLD progression [96], which is supporting with treatment studies' findings of ACEI or ARB on hepatic fibrosis and steatosis [97-99]. In a mechanistic study investigating the interactions between the RAS and the NAFLD, it was determined that ACEIs or ARBs administrations reduce liver stiffness in the patients with NAFLD compared to the control group [97]. Moreover, RAS inhibition may prevent fibrosis progression in the livers of patients with type 2 diabetes [98]. In a experimental study, telmisartan administration decreased triglyceride and HOMA-IR levels and attenuated cytoplasmic degeneration in a rat model of 10% fructose-induced NAFLD [99]. The efficacies of amlodipine, a calcium channel blocker, captopril, an ACE inhibitor, and bezafibrate, an antihyperlipidemic, on hepatic triglyceride levels were compared in a 60% fructose diet-induced NAFLD model. Amlodipine treatment showed no significant effect on hepatic triglyceride and macrovesicular steatosis levels. However, the effects of captopril and bezafibrate on macrovesicular steatosis appeared to be correlated with decreased hepatic triglyceride levels [100]. These findings suggest that fructose-induced NAFLD is involved in abnormal RAS activity.

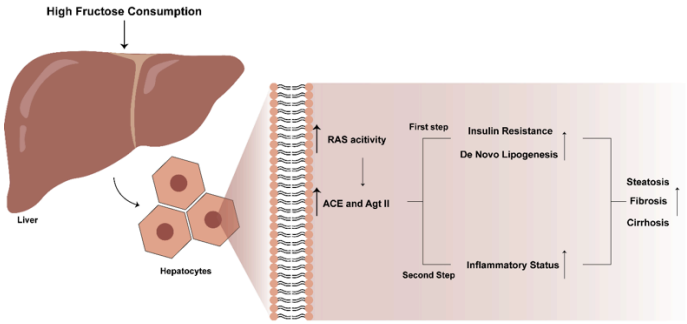

Figure 2. Schematic representation of the development of fatty liver disease due to increased RAS activity with high-fructose consumption. RAS: Renin angiotensin system, Agt II: Angiotensin II, ACE: Angiotensin- converting enzyme

Conclusion

High-fructose consumption may contribute to a significant increase in the prevalence of metabolic syndrome. The activity of systemic and local RAS components has increased in fructose-induced metabolic syndrome. Overexpression of Agt II and AT1R provokes insulin resistance, hypertension, and lipogenesis, leading to the emergence of cardiometabolic complications and NAFLD in fructose-induced metabolic syndrome. Conversely, the reduction in compensatory RAS components including ACE2, Agt 1-7, and AT2R, with fructose consumption exacerbates the complications of the metabolic disorder.

Ethics Approval

Not applicable.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

Contribution of The Authors

Design: A.D., F.A., Literature Search: A.D., F.A., Writing: A.D., F.A. This study has not been published anywhere else.

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